Remarks

The Office Action mailed May 8, 2002, has been received and reviewed. Claims 21-76 remaining withdrawn from consideration, claims 1-20 and 77 having been amended, and claims 78-81 having been added, the claims currently under examination are claims 1-20 and 77-81. Support for the claim amendments and newly added claims is found in the claims as originally filed and throughout the specification. For example, support for amended claim 1 is found in claim 1 as originally filed and at page 3, lines 23-24, page 3, lines 28-29, page 11, line 29, page 14, lines 19-21, and page 15, line 31; support for amended claim 6 is found at page 4, lines 14-16; support for amended claim 7 is found at page 4, line 12; and support for amended claim 8 is found at page 4, lines 14-16. Support for amended claim 77 is found in originally filed claims 1 and 77. Support for new claim 78 can be found on page 11, line 29; support for new claim 79 can be found on page 16, line 1; and support for new claim 80 can be found at page 15, line 32 to page 16, line 1. No new matter is added by these amendments. Reconsideration and withdrawal of the rejections are respectfully requested.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 1-20 and 77 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner asserted that claim 1 is vague and indefinite in the preamble "[a] process to allow the characterization of a microbial gene or genes, here gene." Following the Examiner's suggestion, the recitations "to allow" and "here gene" have been deleted.

The Examiner asserted that claim 1 is vague and indefinite in the recitation "where said gene target is important to the microbe's ability to infect or sustain an infection in an mammal," as it is unclear whether "it is known prior to practicing the claimed method that the gene target is important in the infection process." Amended claim 1 is drawn to a "process for the identification of a microbial gene encoding a gene product that is important to a microbe's ability

to infect or sustain an infection." Thus, it is clear that one need not know before practicing the claimed method whether or not the microbial gene is important to the microbe's ability to infect the host animal.

The Examiner asserted that claim 1, line 11 is vague and indefinite in the recitation "that controls the expression of the target gene or gene product," as it is unclear how the "target gene" and the "gene product" differ from each other. Amended claim 1 is now clearly drawn to only "a target gene product."

The Examiner asserted that the recitation "where said gene, which may be any gene which encodes a microbial protein, or more generally a microbial gene product" in claim 1, lines 15-16 is vague and indefinite in the recitation of a broad range or limitation along with a narrow range or limitation that falls within the broad range or limitation. Claim 1 has been amended to delete this recitation.

The Examiner asserted that claim 1 is vague and indefinite in the recitation "where said mammal is a plurality of at least two mammals with said mammals are initially exposed to tetracycline and infected with said genetically altered microbe," as it is unclear how a single mammal can be a plurality of mammals. Additionally, the Examiner asserted that it was unclear whether the steps of infection and exposure to tetracycline needed to occur at the same time. Amended claim 1 is drawn to a process comprising "infecting a plurality of mammals" and "exposing the plurality of mammals to tetracyline." Thus, it is clear that a "plurality" of mammals is infected. And, as infection and exposure are two separate steps in the claimed process, they need not occur simultaneously.

The Examiner asserted that claim 1 is vague and indefinite in the recitation "meaningful difference between the two groups of animals." This assertion is respectfully traversed. As discussed in the specification on page 4, lines 17-19, "[a] meaningful difference . . . is a mathematically significant difference in the survival rates or levels of microbes, or levels of infection present in the mammals." And, as explained on page 16, lines 18-19 of the specification, such a meaningful difference can be "determined by one [of] ordinary skill in the

art of evaluating microbial infections." Thus, the recitation "a meaningful difference" has a clear meaning to those of ordinary skill in art. The recitation is not vague and indefinite.

The Examiner asserted that claims 2, 4, and 7 are vague and indefinite, as it is not clear if the recitation "is comprised of" is open or closed language. Claims 2, 4, and 7 have been amended to delete these recitations.

The Examiner asserted that claim 5 was vague and indefinite in the recitation "said reporter gene is β-lacatamase." Following the Examiner's suggestion, the claim has been amended to recite "encodes a β-lacatamase."

The Examiner asserted that in claim 6, the metes and bounds of the recitation "additional alterations comprising a tetracycline resistance (or protection) and repressor cassette (TRRDC)" are unclear. Amended claim 6 is drawn to "a tetracycline resistance and repressor DNA cassette (TRRDC), said TRRDC comprising a tetracycline repressor gene and a tetracycline resistance gene," clearly indicating the composition of the TRRDC.

The Examiner asserted that claim 8 is vague and indefinite in the recitation "and where a promoter is operably linked to the TCE," as the organization of the claimed promoter is unclear. Amended claim 8 is drawn to "where the TRRDC promoter is operably linked to the TCE," clearly indicating the organization of the promoter.

The Examiner asserted that claims 9 and 10 are vague and indefinite in the recitation "mathematically significant difference," as it is unclear exactly what constitutes a mathematically significant difference. This assertion is respectfully traversed, as the recitation "a mathematically significant difference" has been deleted form amended claims 9 and 10.

The Examiner asserted that claim 11 the recitation "said significant difference" is vague and indefinite, as the antecedent basis of the recitation in claim 11 or claim 10, from which claim 11 depends, is unclear. Amended claim 11 depends directly from claim 1 and is drawn to a "meaningful difference." The recitation "meaningful difference" has clear antecedent basis in claim 1.

The Examiner asserted that the recitation claim 12 is vague and indefinite in the recitation "is comprised of," as it is unclear whether the recitation is open or closed. Amended claim 12 is drawn to "comprises," recites open language.

The Examiner asserted that claim 13 is vague and indefinite in the recitation "derived from." Following the Examiner's suggestion, to clarify the claimed invention, claim 13 has been amended to recite "obtained from."

The Examiner asserted that claim 14 is vague and indefinite in the recitation "wherein said Tn10 transposon is selected from the sequence of SEQ ID NO:35 and 36," as it is confusing to refer to these two closely related sequences as a single sequence. Additionally, the Examiner asserted it is confusing because SEQ ID NO:35 and SEQ ID NO:36 do not comprise a full transposon. To clarify the claimed invention, amended claim 14 depends from claim 6 and is drawn to "where said TRRDC comprises the sequence of SEQ ID NO:35 or SEQ ID NO:36.

The Examiner asserted that claim 15 is vague and indefinite, as the recitation "said mammals" lacks proper antecedent basis. Amended claim 15, drawn to "where the infected mammals are mice," has proper antecedent basis in claim 1.

The Examiner asserted that claim 16 is vague and indefinite, as the recitation "said recombinant bacterium" lacks proper antecedent basis. Amended claim 16, recites "wherein said genetically altered microbe" and has proper antecedent basis in claim 1.

The Examiner asserted that the recitation "said Staphylococcus species" in claim 17 lacks proper antecedent basis in claim 1. As amended, claim 17 depends from claim 16 and has proper antecedent basis for the recitation "said Staphylococcus species."

The Examiner asserted that claim 77 is incomplete, lacking essential method steps. Applicants respectfully submit that amended claim 77 is drawn to a complete method comprising the steps of "infecting a mammalian host" and "exposing the mammalian host to tetracycline."

The Examiner asserted that claim 77 is vague and indefinite in the recitation "endogenous prokaryotic gene." Amended claim 77 is drawn to "gene product" and no longer recites "endogenous prokaryotic gene."

The Examiner asserted that the metes and bounds of the recitation "controlled amount" in claim 77 are unclear. Claim 77 has been amended to delete the recitation "controlled amount."

In view of the claim amendments made to clarify the claimed invention and the above discussion, it is respectfully submitted that claims 1-20 and 77 particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

The 35 U.S.C. §103 Rejection

The Examiner rejected claims 1, 3, 9-11, and 15-20 under 35 U.S.C. §103(a) as being unpatentable over Bostian et al. (WO 96/49079) in view of Setterstrom et al. (U.S. Patent No. 6,309,669 B1).

Independent claim 1 and dependant claims 3, 9-11, and 15-20 are drawn to a process that comprises infecting mammals "with a microbe that has been genetically altered such that the amount of said gene product produced by said genetically altered microbe is regulated by a Tetracycline-Controllable Element (TCE); . . .*where said genetically altered microbe also comprises a polynucleotide sequence encoding a tetracycline resistance protein* (emphasis added)."

"To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). 'All words in a claim must be considered in judging the patentability of that claim against the prior art.' In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)." See MPEP § 2143.03.

Neither Bostian et al., Setterstrom et al., nor the combination of Bostian et al. in view of Setterstrom et al. teach or suggest a process where the genetically altered microbe also comprises a polynucleotide sequence encoding a tetracycline resistance protein. Thus, Applicants' claims are not taught or suggested by Bostian et al. in view of Setterstrom et al. Withdrawal of the rejection of claims 1, 3, 9-11, 15-10 under 35 U.S.C. §103(a) is respectfully requested.

Summary

It is respectfully submitted that the pending claims 1-20 and 77-81 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Ford et al.

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

26813

PATENT TRADEMARK OFFICE

August 8, 2002
Date

By: Ann M Mueting
Ann M. Mueting
Reg. No. 33,977
Direct Dial (612)305-1217

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: **EL 888274644 US** Date of Deposit: **AUGUST 8, 2002**
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By: Sue Dombroske
Name: Sue Dombroske

APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS
INCLUDING NOTATIONS TO INDICATE CHANGES MADE
Serial No.: 09/600,392
Docket No.: 6137.P US

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted. Additionally, all amendments have been shaded.

In the Claims

For convenience, all pending claims are shown below.

1. [AMENDED] A process for [to allow] the identification [characterization] of a microbial gene [or genes, here gene,] encoding [where said gene encodes] a gene product[; where said gene product is a gene target; where said gene target] that is important to a microbe's ability to infect or sustain an infection in a mammal, which process comprises:

infecting a plurality of mammals with a [where said] microbe [is:] that has been genetically altered [to become a genetically altered microbe,] such that the amount of said gene product produced by said genetically altered microbe is regulated [and controlled] by a Tetracycline-Controllable Element (TCE) [or TCE];

where said TCE is a gene regulatory system that controls the expression of the target [gene or] gene product[,] through its ability to modulate the function of said gene in response to said microbe's exposure to tetracycline, and where said TCE is comprised of a tetracycline-controllable transcription promoter polynucleotide sequence;

[where said gene, which may be any gene which encodes a microbial protein, or more generally a microbial gene product, is regulated by said TCE such that said gene produces either greater or lesser amounts of gene product, depending upon whether or not said genetically altered microbe is exposed to tetracycline;]

where said genetically altered microbe also comprises a polynucleotide sequence encoding a tetracycline resistance protein;

[where] exposing the [said mammal is a] plurality of [at least two or more] mammals [with said mammals are initially exposed] to tetracycline [and infected with said genetically altered microbe];

[followed by: the removal of] once an infection with the genetically altered microbe is established, removing the tetracycline exposure of [exposed to] a portion [of said] of the plurality of mammals, such that a first group of the plurality of mammals is [there is at least mammals one or one group of said mammals] exposed to tetracycline and a second group of the plurality of mammals is [another one or group of] not exposed to tetracycline; and [followed by:

a comparison of] comparing the degree of infection, microbe levels, or [physiological condition] survival rates of the mammals in the first group and the second group [exposed to tetracycline, compared to the degree of infection, microbe levels, or physiological condition of mammals not exposed to tetracycline; followed by:

the identification of said genes, important to a microbe's ability to infect or sustain an infection in a mammal, where the comparison of the mammals exposed to tetracycline compared to the mammals not exposed to tetracycline shows a] wherein a meaningful difference between the two groups of animals identifies the gene product as important to a microbe's ability to infect or sustain an infection in a mammal.

2. [AMENDED] The process of claim 1, where said TCE is [a gene regulatory system that controls the expression of the target gene or gene product, through its ability to modulate the function of said gene in response to said microbe's exposure to tetracycline, and where said TCE is comprised of a tetracycline-controllable transcription promoter polynucleotide sequence,] operably linked to a polynucleotide sequence encoding a reporter gene (RG).

3. [AMENDED] The process of claim [2] 1, where said tetracycline-controllable transcription promoter polynucleotide sequence[,] is a prokaryotic transcription promoter.

4. [AMENDED] The process of claim 1, where said TCE is [a gene regulatory system that controls the expression of the target gene or gene product, through its ability to modulate the function of said gene in response to said microbe's exposure to tetracycline, and where said TCE is comprised of a tetracycline-controllable transcription promoter polynucleotide sequence,]

operably linked to a polynucleotide sequence encoding a reporter gene (RG) and a target gene (TG).

5. [AMENDED] The process of claim 4, where said reporter gene [is] encodes a β-lactamase.

6. [AMENDED] The process of claim 1, where said [microbe has, in addition to the genetic alterations of claim 1, additional genetic alterations comprising] polynucleotide sequence encoding a tetracycline resistance protein is contained on a tetracycline resistance [(or protection)] and repressor DNA cassette (TRRDC), said TRRDC comprising a tetracycline repressor gene and a tetracycline resistance gene.

7. [AMENDED] The process of claim 6, where said TCE is [a gene regulatory system that controls the expression of the target gene or gene product, through its ability to modulate the function of said gene in response to said microbe's exposure to tetracycline, and where said TCE is comprised of a tetracycline-controllable transcription promoter polynucleotide sequence,] operably linked to a polynucleotide sequence encoding a reporter gene (RG) and a target gene (TG) and where the TCE, the TRRDC, the RG, and the TG are all on the same DNA cassette, [which may be] referred to as a Regulatory DNA Cassette [or] (RDC).

8. [AMENDED] The process of claim 6, where [the] said TRRDC promoter is operably linked to the TCE, the tetracycline repressor gene comprises the structural gene *tetM*, and the tetracycline resistance gene comprises the structural gene *tetR* [and where a promoter is operably linked to the TCE].

9. [AMENDED] The process of claim 1, where said meaningful difference between the two groups of animals is a [mathematically significant] meaningful difference in the [survival rates or the] levels of microbes or levels of infection present in the mammals.

10. [AMENDED] The process of claim [9] 1, where said meaningful difference between the two groups of animals is a [mathematically significant] meaningful difference in the survival rates of the groups of animals.

11. [AMENDED] The process of claim [10] 1, where said [significant] meaningful difference between [in] the two [survival rates of the] groups of animals shows that animals exposed to tetracycline have poorer health, higher rates of infection, lower survival or higher levels of microbes than animals not exposed to tetracycline.

12. [AMENDED] The process of claim [7] 6, where [the] said tetracycline resistance [resistent] gene of said TRRDC [is comprised of] comprises sequences from the *Staphylococcus aureus tetM* gene.

13. [AMENDED] The process of claim [12] 6, where said tetracycline repressor gene of said TRRDC is obtained [derived] from the Tn10 transposon.

14. [AMENDED] The process of claim [13] 6, where said [Tn10 transposon is selected from] TRRDC comprises the sequence of SEQ[.] ID[.] NO[.]: 35 [and] or SEQ ID NO:36.

15. [AMENDED] The process of claim 1, where said infected mammals are mice.

16. [AMENDED] The process of claim 1, where[in] said [recombinant bacterium] genetically altered microbe is a Staphylococcus species.

17. [AMENDED] The process of claim 16 [1], where[in] said Staphylococcus species is *Staphylococcus aureus*.

18. [AMENDED] The process of claim 1, where[in] said microbe is a virus.

19. [AMENDED] The process of claim 1, where[in] said microbe is a lower eukaryote.

20. [AMENDED] The process of claim 1, where[in] said microbe is a yeast.

77. [AMENDED] A process to regulate expression of a[n endogenous prokaryotic] gene [comprising the cultivation of the prokaryotic cell] product by a microbe in a mammalian host with [a controlled amount of] tetracycline or a tetracycline analog, said process comprising:

infecting a mammalian host with a microbe that has been genetically altered such that the amount of said gene product produced by said genetically altered microbe is regulated by a Tetracycline-Controllable Element (TCE);

where said TCE is a gene regulatory system that controls the expression of the target gene product through its ability to modulate the function of said gene in response to said microbe's exposure to tetracycline, and where said TCE is comprised of a tetracycline-controllable transcription promoter polynucleotide sequence;

where said genetically altered microbe also comprises a polynucleotide sequence encoding a tetracycline resistance protein; and

exposing the mammalian host to tetracycline.

78. [NEW] The process of claim 77, further comprising, once an infection with the genetically altered microbe is established, removing the tetracycline exposure of the mammalian host.

79. [NEW] The process of claim 1, where said plurality of mammals are exposed to tetracycline while being infected with the genetically altered microbe.

80. [NEW] The process of claim 1, where said plurality of mammals are exposed to tetracycline by adding tetracycline to the drinking water.

81. [NEW] The process of claim 2, where said reporter gene encodes a β-lactamase.